Towards sustainable management of arboviral diseases

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Long-term chikungunya sequelae in Curaçao: burden, determinants and a novel classification tool

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Abstract

Background

Beyond the acute illness phase, chikungunya constitutes a public health problem given its chronic disease phase, which may include long-term arthralgia, arthritis, fatigue and depression. Currently, there is no consensus on how to define chikungunya chronicity.

Methods

A comprehensive cross-sectional survey was performed in Curaçao in June-July 2015 to evaluate 304 adult laboratory-confirmed chikungunya patients 3-16 months after diagnosis. We developed a novel tool, the Curaçao Long-Term Chikungunya Sequelae (CLTCS) Score to classify chronic chikungunya disease, and estimate its burden regarding disease duration, clinical presentation and impact on quality of life (QoL).

Results

Disease persistence was estimated to be 79% one month after symptom onset and 64% after 400 days. Chikungunya persistence was characterized by higher proportions of arthralgia, weakness, myalgia and age between 41-60 years. Individuals were classified as 'highly affected', 'mildly affected' and 'recovered'. 'Highly affected' disease status was associated with clinical complaints (arthralgia, weakness, loss of vitality, and being diabetic) and major decreases in QoL scores.

Conclusion

In the Caribbean, a high proportion of chikungunya patients remain chronically affected. We propose the CLTCS as a suitable score to easily and rapidly classify the severity of chikungunya chronic disease, and to assess the need for symptom-alleviating treatment.

Introduction

Chikungunya is a viral vector-borne disease transmitted by the day-biting mosquitoes Aedes aegypti and Ae. albopictus [1]. The disease has become a global health problem of increasing importance given its recent rapid spread and the extent and impact of chronic disease. To date, the literature lacks consensus on how to define chronic chikungunya disease.

The first locally acquired chikungunya cases in the Caribbean island of Saint Martin in December 2013 indicated the introduction of chikungunya virus (CHIKV) in the Americas, which resulted in over one million confirmed or suspected cases throughout the continent [2-4].

In Curaçao, the epidemic of chikungunya became evident in June/July 2014. The explosive behaviour of this epidemic resulted in 835 reported laboratory-confirmed cases and thousands of clinical cases by October 2014 [4]. These accumulated to an estimated 50,000-75,000 by the end of the outbreak in January 2015 (IG, unpublished).

Chikungunya disease typically manifests itself with an abrupt onset of high fever, headache, in a certain percentage with rash, and almost invariably musculoskeletal pain with predominantly incapacitating arthralgia. Treatment of the disease is purely symptomatic, focusing on pain relief through the use of non-steroidal anti-inflammatory drugs [1]. Although the acute phase of chikungunya could be considered as relatively short (7-10 days), the disease commonly evolves into a sub-acute (< 3 months) or chronic (> 3 months) phase. The latter has been characterized by long-lasting relapsing or lingering rheumatic musculoskeletal pain, arthralgia, fatigue, and depression [5-8]. Notwithstanding the wide range of symptoms that chikungunya can cause, research mainly focuses on musculoskeletal manifestations when investigating persistence of chikungunya, thereby neglecting other disease manifestations [9]. Studies estimate that up to 60% of chikungunya patients remain symptomatic 12-36 months after infection [8,10-12]. After five years, up to 12% of the infected population might still report chikungunya-related symptoms [13-15].

It seems likely that the chronic phase of chikungunya can cause a significant decrease in quality of life (QoL), becoming an important and under-estimated public health problem [10,16]. However, to date, research on QoL related to chikungunya chronicity remains scarce and especially lacks a thorough description combined with musculoskeletal, psychological and neurological manifestations.

The aim of this study was (1) to estimate the burden of the first chikungunya outbreak in Curaçao in terms of symptoms and duration of chronic disease, and the impact on QoL 3-16 months after diagnosis; (2) to develop a practical tool to classify chronic chikungunya disease; and (3) to identify factors associated with mild to highly chronically affected individuals.

Study methods

Study design and population

Following the chikungunya epidemic of 2014-2015 in Curaçao, a cross-sectional survey of adult subjects with a confirmed chikungunya infection diagnosed during the epidemic was performed between June and July 2015. Chikungunya infection was confirmed based on diagnosis of a general practitioner including a laboratorial assessment outcome of either a positive IgM or IgG (since this was the first documented chikungunya epidemic in Curaçao), positive reverse transcription polymerase chain reaction (RT-PCR) or positive indirect fluorescent antibody (IFA). ELISA (ELISA: IBL, Germany) was performed by the Analytical Diagnostic Centre (ADC N.V.) in Curaçao according to the manufacturers' protocol. Assessment by RT-PCR or IFA concerned samples transferred to the National Institute for Public Health and the Environment of The Netherlands (RIVM). Twenty general practitioners working in 14 different practices representative of the population of Curaçao, both geographically and socio-economically, provided patient data. The selected subjects were either contacted by phone or visited at their residence for inclusion. Those consenting to participate were interviewed at home.

Study site

Curaçao is an island in the southern Caribbean Sea with a surface of 444 km2 and approximately 150,000 inhabitants. The population of Curaçao is mainly concentrated in the capital, Willemstad [16]. Curaçao has a semi-arid climate with a rainy season from September to January and a dry season from February to August [17].

Data collection

Study participants were interviewed using a questionnaire containing pre-coded and open questions on socio-demographic characteristics (Table 1). Experienced local interviewers working for the Central Bureau of Statistics of Curaçao (CBS) and speaking Papiamentu, Dutch, English and Spanish performed the interviews. The questionnaire was prepared in Dutch, piloted, corrected, and translated into Papiamentu, Spanish and English.

Subjects were asked to provide the date of onset of the acute chikungunya episode and the duration of symptoms and complaints. They were asked if they (still) suffered from the pre-coded symptoms at the time of interview to which they could answer 'yes', 'somewhat', or 'no' (Supplementary Tables 1, 2). Finally, participants were asked to fill in a RAND-36 (SF-36) questionnaire in order to assess their current Quality of Life (QoL) [19,20]. The RAND-36 was used because this tool provides a short but comprehensive assessment of QoL, including physical and emotional dimensions of health, and was previously applied to the population of Curaçao [21].

Table 1. Socio economic characteristics of the study population, stratified by chronic disease status applying the CLTCS Score

	Total (n=304)		Recovered (n=110)		Mildly affected (n=105)		Highly affected (n=89)		p-value[a]
Age	n	(%)	n	(%)	n	(%)	n	(%)	
18-40 years	66	(21.7)	36	(32.7)	17	(14.6)	13	(14.6)	
41-60 years	158	(52.0)	44	(40.0)	63	(57.3)	51	(57.3)	
>60 years	80	(26.3)	30	(27.3)	25	(23.8)	25	(28.1)	**0.005**
Sex									
Female	225	(73.0)	76	(69.1)	75	(71.4)	74	(83.1)	
Male	79	(26.0)	34	(30.9)	30	(28.6)	16	(16.9)	0.061
Education									
Illiterate/ primary school	70	(23.0)	25	(22.7)	24	(22.9)	21	(23.6)	
Secondary school	110	(36.2)	36	(32.7)	35	(33.3)	39	(43.8)	
Intermediate vocational education	80	(26.3)	33	(30.0)	32	(30.5)	15	(16.9)	
University (of applied sciences)	44	(14.5)	16	(14.5)	14	(13.3)	14	(15.7)	0.367
Occupation[b]									
Unemployed/student/housewife/ voluntary	58	(19.1)	19	(17.4)	18	(17.1)	21	(23.6)	
Paid job (domestic or manual)	129	(42.6)	42	(38.5)	50	(47.6)	37	(41.6)	
Paid job (not domestic or manual)	61	(20.1)	28	(25.7)	20	(19.0)	13	(14.6)	
Retired	55	(18.2)	20	(18.3)	17	(16.2)	18	(20.2)	0.435
Income[c,d]									
0-999 ANG	30	(10.1)	7	(6.5)	16	(15.4)	7	(8.0)	
1000-2499 ANG	121	(40.6)	40	(37.4)	41	(39.4)	40	(46.0)	
2500-4999 ANG	110	(36.9)	43	(40.2)	36	(34.6)	31	(35.6)	
>5000 ANG	37	(12.4)	17	(15.9)	11	(10.6)	9	(10.3)	0.265
Underlying chronic disease									
Absence of underlying disease	152	(50.0)	61	(55.5)	60	(57.1)	31	(34.8)	**0.003**
Joint disease	42	(13.8)	8	(7.3)	14	(13.3)	20	(22.5)	**0.008**
Cardiovascular disease[e]	73	(24.0)	20	(18.2)	26	(24.8)	27	(30.3)	0.133
Neurologic disease	11	(3.6)	4	(3.6)	4	(3.8)	3	(3.4)	1.000*
Diabetes mellitus	39	(12.8)	10	(9.1)	8	(7.6)	21	(23.6)	**0.001**
Other diseases[f]	30	(9.9)	13	(11.8)	6	(5.7)	11	(12.4)	0.209

**Fisher's exact test; ap-value corresponds to the comparison of the proportions between the groups recovered, mildly affected and highly affected; bTotal recovered group n=109; cTotal recovered group n=107, total mildly affected group n=104, total highly affected group n=87; dAntillian Guilder; 1 ANG = 0.56 USD eCardiovascular disease group includes hypercholesterolemia and hypertension; fOther diseases includes chronic lung diseases, thyroid diseases, auto-immune diseases, gastro-intestinal complaints, unspecified pain, allergies and other.*

Severity of chronic chikungunya disease – development of a novel classifying system

To classify chronicity of chikungunya disease, subjects were asked whether they still perceived complaints of chikungunya at the time of interview. Thenceforth, four standard statements were assessed with a five-point scoring scale (Table 2). Cronbach's Alpha Test, which assesses the reliability, or internal consistency, of the four-statement scale yielded a high score (0.891). Subsequently, a severity score was obtained by summing-up the scores of the four questions. This score was categorized into 'recovered' (score=4), 'mildly affected' (score=5-12) and 'highly affected' (score=13-20) (Supplementary Table 3). Hereinafter, we refer to this score as the Curaçao Long-Term Chikungunya Sequelae (CLTCS) Score.

Table 2. CLTCS Score assessment form

Please, check the box according to how much you agree or not with the following statements:	Do not agree at all 1	2	3	4	Fully agree 5
1. I am fully functional again after having had chikungunya.....	☐	☐	☐	☐	☐
2. I don't have chikungunya complaints any more	☐	☐	☐	☐	☐
3. I still feel the effects of chikungunya disease every day.....	☐	☐	☐	☐	☐
4. The chikungunya effects seem to return again and again in my case.....	☐	☐	☐	☐	☐

Using the CLTCS (long-term chikungunya sequelae) Score to assess chronic chikungunya disease. Perform the following steps:

1. Ask the patient to fill in the form; all answers are required.

2. Recode the scores of question 1 & 2 as follows: 5=1; 4=2; 3=3; 2=4; 1=5.

3. After recoding, sum the scores of questions 1, 2, 3 & 4 to obtain the CLTCS Score.

4. Classify chikungunya chronic disease status:

- *Recovered (no complaints) = 4*
- *Mildly affected = 5-12*
- *Highly affected = 13-20*

Data analysis

Data was entered into a database using SPSS Data Entry Station (SPSS Inc. 1996-2003, version 4.0.0). Data was checked for consistency and analysed anonymously. Based on their neighbourhood, participants were allocated to geozones [17]. The distribution of the study population was analysed and presented in a map using ArcGIS (ArcGIS Desktop: Release 10.3. Redlands, CA: Environmental Systems Research Institute). Chi-square test or Fisher's exact test was used to test associations between categorical variables. Continuous variables were converted into ordered categorical variables when suitable. For normally distributed quantitative data, means were compared using Students t-test or ANOVA; for skewed distributions, the Mann-Whitney U or Kruskal Wallis test was used. A survival curve was created using the Kaplan-Meier

estimator. A multivariate binary logistic regression was performed to describe characteristics of chronic chikungunya disease. General characteristics and symptoms ('no' vs. 'somewhat' plus 'yes') with a p-value ≤0.2 in the univariate analysis were included in a multivariate model to test their influence on disease status. Variables with highest p-values were eliminated backwards, until all variables in the model showed significance. Significance was determined at 5% level. Data was analysed using SPSS (SPSS Inc., version 22.0, Chicago, Illinois).

Ethical committee approval

The study was approved by the Medical Ethical Board of the Sint Elisabeth Hospital (METC SEHOS) Curaçao (Reference number: 2015-002). All the participants who entered this study signed a written informed consent.

Description of the study population

A total of 411 participants with a recent acute chikungunya infection were contacted and invited to join the study, of which 339 consented and participated (response rate 82.5%). The reasons for non-contacting and non-response are summarized in Supplementary Table 4. Of the 337 participants, 304 had a laboratory-confirmed CHIKV infection and were included in this study. Date of onset of acute chikungunya disease ranged from April 2014 – March 2015, i.e. 92-460 days before the interview. The socio-demographic characteristics and comorbidity of the study population are summarized in Table 1. The participants' age range was 18-94 years (Quartile (Q)1=41 years; median=51 years; Q3=61 years). Most participants were female (n=225; 74.0%), and 40.8% (n=124) had an educational level of intermediate vocational education or university. The majority had a paid job (n=190; 62.7%) and approximately half of the participants had an income up to 2500 ANG (Antillean Guilder; 1 ANG = 0.56 USD). Forty-seven (72.3%) of all 65 geozones [17] of Curaçao were represented in this study. Figure 1 shows the proportion of participants per 1,000 inhabitants per geozone.

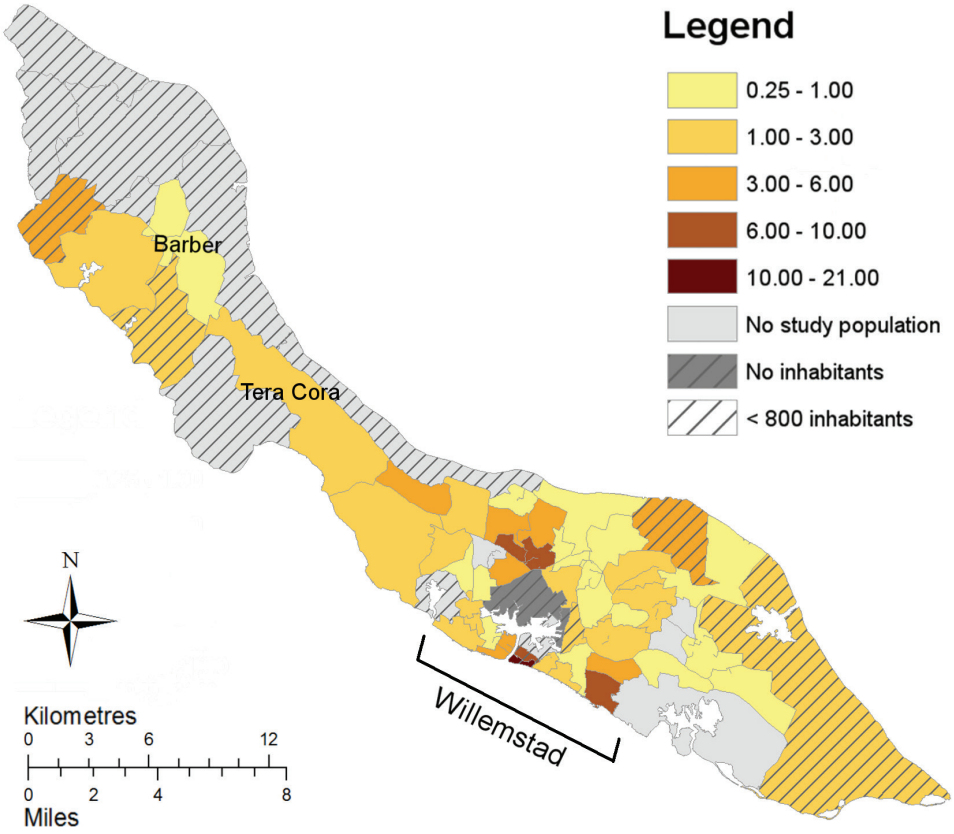

Figure 1. Distribution of the study population among geozones of Curaçao (cases per 1,000 inhabitants)
Willemstad (capital) covers the indicated area from the south to the north of Curaçao.

Chikungunya chronic disease status

To characterize chikungunya chronic disease status, the CLTCS Score was developed (see Methods, Data collection). This score was stratified in three categories: 'recovered', 'mildly affected' and 'highly affected'. The classification showed consistency with the 'yes or no'-question regarding chronic disease persistence (Supplementary Table 3). Therefore, the population of this study is further described using the new classification system, i.e. the CLTCS Score.

Duration of chikungunya disease

At the time of interview, 36.2% (n=110) were defined as fully recovered from chikungunya, while the remaining 63.8% (n=194) were defined as still being mildly affected (n=105, 34.5%) or highly affected (n=89; 29.3%) by chronic chikungunya disease. The 'recovered' study population estimated their disease duration between 1-240 days (n=107; Q1=14 days; median=30 days; Q3=90 days; Figure 2). The 'mildly affected' population reported an ongoing disease duration of 273 days on average, ranging from 94 – 426 days (n=105; SD=69.4). Finally, the 'highly affected' population reported having complaints for 267 days on average, ranging from 101 – 422 days (n=89; SD=55.8). Out of the 304 individuals, sixty-two (20.6%) reported to be fully recovered from chikungunya within one month (Figure 2). Figure 2 shows the probability to remain affected with chronic chikungunya disease over time. The model estimates that in 79.4% (95% CI: 83.9%-74.9%) of patients, long-term sequelae persist after a month, and in 64.0% (95% CI: 69.5%-58.5%) after 400 days.

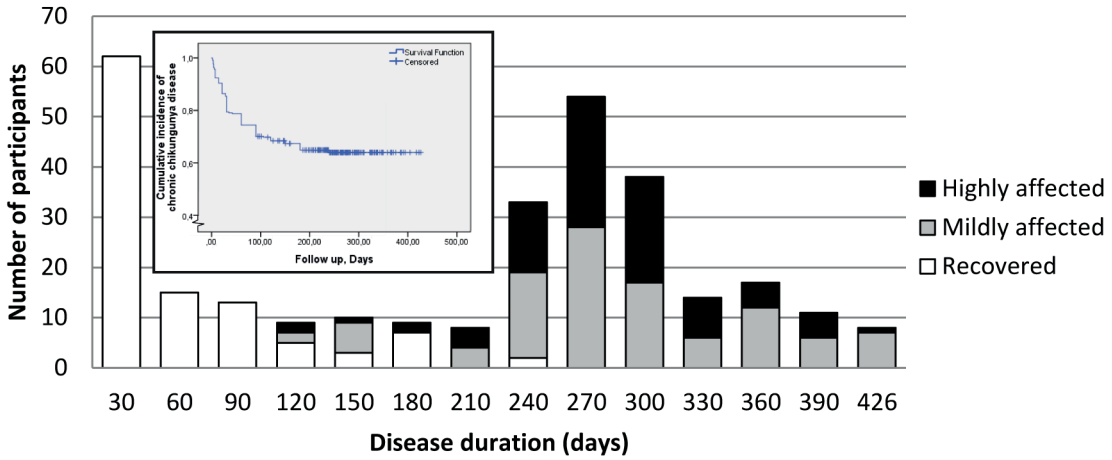

Figure 2. Distribution of disease status duration and cumulative incidence of disease persistence

The horizontal axis shows the maximum duration of disease (days) of the specific category; the number of subjects is expressed in the vertical axis. The recovered population is shown in white, the still mildly/highly affected population is shown in grey/black. The disease duration of the mildly/highly affected population is the time between disease onset and interview (ranging from 92-460 days), meaning that chronic disease was ongoing and may last longer than presented here. The Kaplan-Meier curve presents the cumulative incidence of disease persistence by follow-up time.

Symptoms of chronic chikungunya disease

Symptoms present at the time of interview were assessed. Subjects that answered 'somewhat' or 'yes' were recorded as symptomatic. These were stratified by chronic disease status and compared (Figure

3). All symptoms showed a significant association with disease status (Supplementary Table 5). The total data on the (severity of) symptoms is shown in Supplementary Tables 1, 2. The most frequently reported symptoms within the mildly and highly affected population were arthralgia and weakness in the upper or lower extremities, myalgia and tiredness. Other symptoms significantly associated with mildly or highly affected subjects were arthralgia and weakness in the back/neck, insomnia, sombreness, loss of vitality, numbness, paraesthesia (tingling), nausea, vomiting, abdominal pain and hair loss.

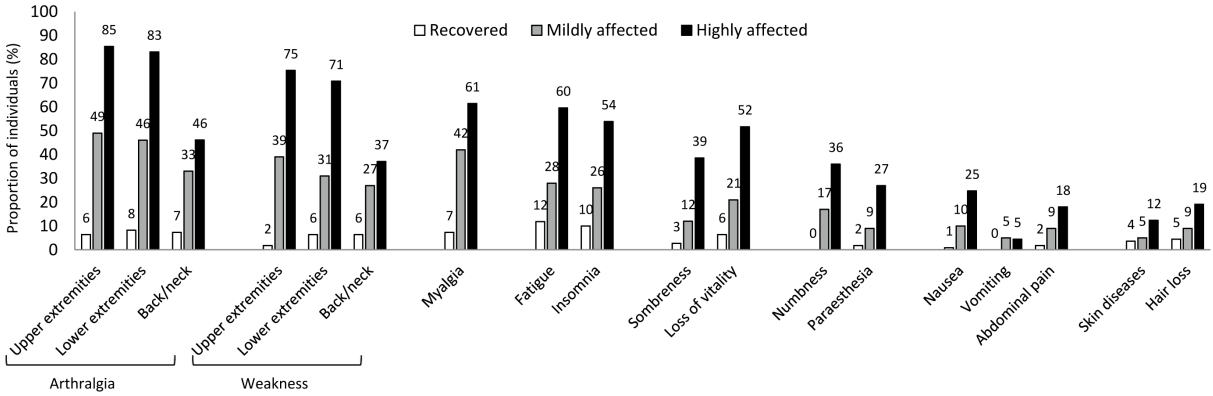

Figure 3. Symptoms of chronic chikungunya stratified by chronic disease status (CLTCS Score)

Determinants of chronic chikungunya disease status

To characterize the different chronic chikungunya disease statuses, the 'recovered' population vs. the 'affected' population (mildly plus highly affected groups) and the mildly vs. highly affected groups were compared in univariate analyses (Supplementary Tables 1,2,6,7) and a binary multiple logistic regression. Supplementary Tables 8 and 9 show the general characteristics and symptoms independently associated with chronic chikungunya disease status. Individuals with chronic chikungunya disease were more likely to have arthralgia in upper (OR=4.9; p=0.002) and/or lower extremities (OR=12.3; p<0.001), weakness in upper extremities (OR=14.9; p=0.001) and myalgia (OR=3.1; p=0.030), and an age of 41-60 years (p=0.007) compared to recovered subjects. Within the non-recovered subjects, the highly affected individuals were distinguished from the mildly affected by presenting more frequently arthralgia in upper (OR=7.0; p<0.001) and/or lower extremities (OR=3.3; p=0.015), weakness in lower extremities (OR=4.2; p=0.005) and loss of vitality (OR=3.5; p=0.004); and having a history of diabetes (OR=3.7; p=0.013). Being mildly affected was mainly associated with reporting weakness in the back or neck (OR=6.67; p=0.001) compared to the highly affected.

Quality of life of a population with chronic chikungunya symptoms

Figure 4 shows the influence of chronic chikungunya disease on the QoL measured with the RAND-36 questionnaire. RAND-36 scores range from 0-100 and higher scores reflect better health outcomes. The recovered population showed the highest scores on all QoL dimensions, followed by the mildly affected and the highly affected population respectively (p≤0.001; Kruskal-Wallis test). Supplementary Table 10 provides the total data on RAND-36 QoL score of this population.

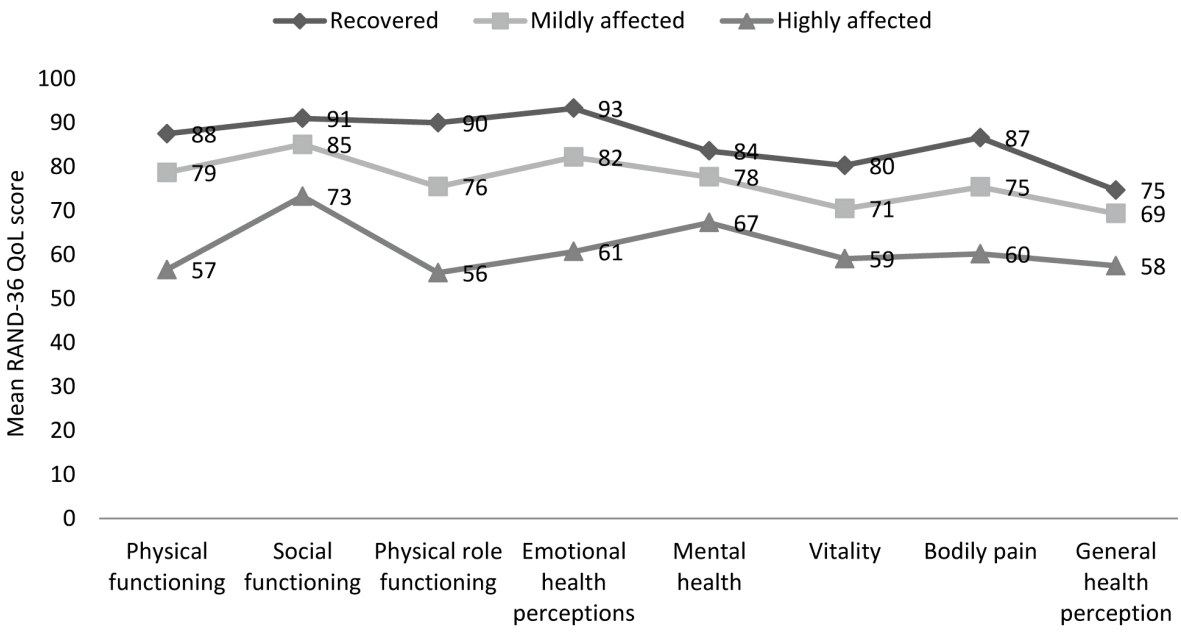

Figure 4. Mean scores RAND-36 QoL by chronic disease status

Physical role function= (daily life) role limitations due to physical health

Discussion

A cross-sectional study including 304 individuals with a laboratory-confirmed recent chikungunya infection was conducted to assess the duration, symptomatology and impact on the quality of life (QoL) of chronic chikungunya disease in Curaçao. This study provides comprehensive insights into the different degrees, clinical extent and associated factors of chronic chikungunya disease. Furthermore, it introduces the CLTCS Score, an easy and fast instrument for health workers to characterize the severity grades of chronic chikungunya in their patients.

The CLTCS Score was developed and applied to characterize chronic chikungunya disease. Compared to other published arthritis assessment instruments (e.g. the Health Assessment Questionnaire (HAQ) [23], Arthritis Impact Measurement Scales (AIMS) [22], Rheumatiod Arthritis Severity Scale (RASS) [24]), the CLTCS Score is swifter to use (than e.g. the HAQ, AIMS) and captures the broad clinical presentation of chikungunya (unlike the RASS, HAQ). Most studies describe chronic chikungunya disease based on rheumatic manifestations, classifying individuals binary as '(clinically) recovered' vs 'not recovered' with self-reported recovery of chikungunya disease [25,26] or presence of (self-perceived) persistent/relapsing rheumatic manifestations [8,10,27,28] as criterion. The CLTCS Score differs from most of these approaches by comprehensively assessing the patient and not solely focusing on the presence of rheumatic disease (mainly arthralgia). We believe that this score enables the health care worker to estimate the severity of chikungunya symptoms quickly but accurately. As a consequence, using the CLTCS Score, 64% of our study population was defined as chronically affected, compared to the 51% who referred being affected when using simpler classification methods ('recovered' vs. 'affected') (Supplementary Table 3). The results of the present study imply that previous classifications might underestimate disease persistence.

Previous studies, as recently reviewed by van Aalst and colleagues [9], have shown that in 18-60% of the individuals chronic chikungunya persisted for a period of 12-36 months [8,10,11,12] while in 2-12% of the subjects chronic disease may last for up to 5 years or longer [13-15]. Our study showed a relatively high proportion of disease persistence amongst the population, on the basis of our classification method of chronic chikungunya. In our study population, 20.6% were defined as fully recovered within one month. Consistent with another study [27], the Kaplan-Meier estimate (Figure 2) showed a 64% chance of disease persistence for over 400 days. Disease persistence remained at the same proportions between 90 and 400 days (Figure 2). Likewise, the contribution of the highly affected to the total study population demonstrated a constant level (Figure 2). This implies that those who may suffer from severe disease for a longer period, might be already identified three months after disease onset using the CLTCS Score.

A wide range of chronic symptoms was associated with the different disease statuses (Supplementary Table 5). All symptoms except for 'vomiting', showed a higher proportion and severity in the highly affected group (Supplementary Table 2,5). The affected individuals reported most frequently musculoskeletal symptoms, corresponding with other studies [8,10,12,25-28), but a considerable proportion referred concomitant tiredness, sleeplessness and neuropsychological symptoms [12,16,26,29]. The importance of

the scarcely described neurologic chronic manifestations associated with CHIKV [30-32] was demonstrated in this study.

This study is the first to assess the RAND-36/SF-36 QoL questionnaire combined with a wide range of symptoms. The symptoms associated with chronic disease statuses are likely to explain the differences in QoL. The QoL scores of the recovered group were comparable with or higher than those of a normal population, in contrast to the decrease in scores in all domains of the mildly affected population, and a major decrease in QoL in the highly affected group. The QoL scores of our 'recovered' group of individuals were also comparable to those of 'healthy normal' individuals as observed in a previous study in Curaçao (Supplementary Table 10) [21]. This consistency between a chikungunya-'recovered' population and a 'healthy normal' population was shown before [25], indicating that subjects in a 'recovered' group might serve as a control group when assessing chronic chikungunya sequelae. The latter is in particular relevant for areas with high attack rates during chikungunya outbreaks like in Curaçao, where 33-50% of the population was infected in the first chikungunya epidemic. A chikungunya-negative 'healthy normal' control group is hard to recruit in such situations. That notwithstanding, lack of inclusion of this 'healthy normal' group is still considered as a limitation of this study.

RAND-36 measured QoL scores were highly associated with chronic disease statuses. This is consistent with other studies using the RAND-36/SF-36 QoL questionnaire [10,25,29], while a study using the (shorter QoL questionnaire) SF-12 found a moderate impact on physical, but no impact on mental status [16]. Generally, a difference of 5-10 points in the domains of the RAND-36 is considered to be a Minimally Clinical Important Difference (MCID) [33-36]. The major drop in QoL scores from the highly affected population exceeds the 10-point border on all domains when compared with the QoL scores of the recovered (score difference: 16-34) and the mildly affected population (score difference: 10-22) (Figure 4, Supplementary Table 10). This finding is alarming and stresses the importance of identifying and treating these 'highly affected' patients early and appropriately. However, the decrease in QoL of the 'mildly affected' individuals is considerably less (Figure 4) and implies that, although a MCID on QoL can still be achieved on some of the QoL domains, no intensive monitoring is needed for this group. Consequently, efficient psychological and physical care for chronic chikungunya patients should focus on the highly affected group.

This study investigated the characteristics that differentiate the severity of chronic chikungunya disease status. The main characteristics associated with a (highly) affected disease status were higher proportions of arthralgia and weakness in the extremities. Other studies show higher proportions of rheumatic manifestations in older participants [12,25,37], which is in line with the data from our study. However, participants older than 60 years had a higher chance to be defined as recovered of chronic chikungunya than those between 41-60 years old; implying that rheumatic manifestations in individuals older than 60 years may have been less often attributed to a previous chikungunya infection. For example, arthrosis/arthritis (degenerative/inflammatory joint disease) may be responsible for chronic joint complaints of those stating to be recovered of chikungunya while remaining with joint pain. Hence, classification methods of chronic chikungunya sequelae in future studies should not solely hinge on articular manifestations, or explicitly control for articular/rheumatic comorbidities. The described characteristics associated with disease status

contribute to the understanding of which conditions and symptoms make patients perceive their chronic chikungunya disease as severe. Accordingly, physicians should be aware that chronic chikungunya patients presenting with the above-mentioned characteristics as well as loss of vitality and having diabetes, have a higher risk of being highly affected.

The recruitment procedure of this study via general practitioners resulted in a study population who is known by their physicians for their CHIKV infection, which might have implications for the generalizability of the study. The study population consisted of 26.0% of males, compared to 45.7% males in the total population of Curaçao [17]. Results on QoL and symptoms might differ if assessed in more gender-balanced studies, since females tend to assess their QoL lower than males [38]. The higher percentage of females in this study might be explained by the findings that they visit a doctor more often [39]. Nonetheless, selection bias was limited given the high response rate of this study (82.5%). Further limitations of this study which should be taken into account are the following: co-infections (e.g. dengue) were not excluded, the assessment of onset of chikungunya disease (at time of interview) might have led to recall bias, time between disease onset and time of interview differed, and the different interviewers performing the interviews may have induced investigator bias. The strengths of this study were its comprehensive nature and the availability of extensive qualitative data, which gave the researchers a wider context to interpret the results. Patients were visited and surveyed at home, providing a safe and confident environment. Moreover, the study population is representative of the neighbourhoods, nationalities and socio-economic classes of the whole island (Figure 1).

In conclusion, this study characterized chikungunya chronic disease into 'recovered', 'mildly affected' and 'highly affected'. The symptoms and major impact on QoL associated with this classification plead to prioritize the highly affected group in chronic chikungunya care. This group can easily be identified using the CLTCS score (presented and explained in Table 2).

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Supporting information

Supplementary table 1. Univariate analysis of clinical presentation comparing recovered vs. affected population

	Total (n=304)						Recovered (n=110)						Affected (n=194)						
	No		Yes				No		Yes				No		Yes				p-value[a]
			Somewhat		Yes				Somewhat		Yes				Somewhat		Yes		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Joint pain in the …																			
upper extremities	170	(55.9)	72	(23.7)	62	(20.4)	103	(93.6)	4	(3.6)	3	(2.7)	67	(34.5)	68	(35.1)	59	(30.4)	**<0.001**
lower extremities	173	(56.9)	62	(20.4)	69	(22.7)	101	(91.8)	2	(1.8)	7	(6.4)	72	(37.1)	60	(30.9)	62	(32.0)	**<0.001**
back/neck	220	(72.4)	46	(15.1)	38	(12.5)	102	(92.7)	4	(3.6)	4	(3.6)	118	(60.8)	42	(21.6)	34	(17.5)	**<0.001**
Weakness in the …																			
upper extremities	194	(63.8)	67	(22.0)	43	(14.1)	108	(98.2)	1	(0.9)	1	(0.9)	86	(44.3)	66	(34.0)	42	(21.6)	**<0.001**
lower extremities	201	(66.1)	54	(17.8)	49	(16.1)	103	(93.6)	4	(3.6)	3	(2.7)	98	(50.5)	50	(25.8)	46	(23.7)	**<0.001**
back/neck	236	(77.6)	34	(11.2)	34	(11.2)	103	(93.6)	4	(3.6)	3	(2.7)	133	(68.6)	30	(15.5)	31	(16.0)	**<0.001**
Myalgia[b]	197	(65.0)	65	(21.5)	41	(13.5)	102	(92.7)	6	(5.5)	2	(1.8)	95	(49.2)	59	(30.6)	39	(20.2)	**<0.001**
Fatigue	209	(68.8)	56	(18.4)	39	(12.8)	97	(88.2)	8	(7.3)	5	(4.5)	112	(57.7)	48	(24.7)	34	(17.5)	**<0.001**
Insomnia	218	(71.7)	49	(16.1)	37	(12.2)	99	(90.0)	6	(5.5)	5	(4.5)	119	(61.3)	43	(22.2)	32	(16.5)	**<0.001**
Sombreness[b]	253	(83.5)	31	(10.2)	19	(6.3)	107	(97.3)	2	(1.8)	1	(0.9)	146	(75.6)	29	(15.0)	18	(9.3)	**<0.001**
Loss of vitality	229	(75.3)	51	(16.8)	24	(7.9)	103	(93.6)	6	(5.5)	1	(0.9)	126	(64.9)	45	(23.2)	23	(11.9)	**<0.001**
Numbness	254	(83.6)	32	(10.5)	18	(5.9)	110	(100.0)	0	(0.0)	0	(0.0)	144	(74.2)	32	(16.5)	18	(9.3)	**<0.001**
Paraesthesia	269	(88.5)	20	(6.6)	15	(4.9)	108	(98.2)	1	(0.9)	1	(0.9)	161	(83.0)	19	(9.8)	14	(7.2)	**<0.001**
Nausea	271	(89.1)	23	(7.6)	10	(3.3)	109	(99.1)	1	(0.9)	0	(0.0)	162	(83.5)	22	(11.3)	10	(5.2)	**<0.001**
Vomiting[b]	294	(97.0)	5	(1.7)	4	(1.3)	110	(100.0)	0	(0.0)	0	(0.0)	184	(95.3)	5	(2.6)	4	(2.1)	**0.029***
Abdominal pain[c]	276	(91.1)	20	(6.6)	7	(2.3)	107	(98.2)	2	(1.8)	0	(0.0)	169	(87.1)	18	(9.3)	7	(3.6)	**0.001**
Skin diseases	284	(93.4)	11	(3.6)	9	(3.0)	106	(96.4)	3	(2.7)	1	(0.9)	178	(91.8)	8	(4.1)	8	(4.1)	0.119
Hair loss	273	(89.8)	12	(3.9)	19	(6.3)	105	(95.5)	3	(2.7)	2	(1.8)	168	(86.6)	9	(4.6)	17	(8.8)	**0.014**

**Fisher's exact test; ap-value corresponds to the comparison of the proportion of individuals answering 'yes' (proportion of individuals answering 'somewhat' and 'yes' summed) and those responding 'no' between the groups 'recovered' and 'affected' (mildly and highly affected groups pooled together); bTotal affected group n=193; cTotal recovered group n=109*

Supplementary table 2. Univariate analysis of clinical presentation comparing mildly affected vs. highly affected

	Mildly affected (n=105)						Highly affected (n=89)						
	No		**Yes** Somewhat		Yes		**No**		**Yes** Somewhat		Yes		p-value[a]
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Joint pain in the …													
upper extremities	54	(51.4)	38	(36.2)	13	(12.4)	13	(14.6)	30	(33.7)	46	(51.7)	**<0.001**
lower extremities	57	(54.3)	31	(29.5)	17	(16.2)	15	(16.9)	29	(32.6)	45	(50.6)	**<0.001**
back/neck	70	(66.7)	26	(24.8)	9	(8.6)	48	(53.9)	16	(18.0)	25	(28.1)	0.070
Weakness in the …													
upper extremities	64	(61.0)	32	(30.5)	9	(8.6)	22	(24.7)	34	(38.2)	33	(37.1)	**<0.001**
lower extremities	72	(68.6)	25	(23.8)	8	(7.6)	26	(29.2)	25	(28.1)	38	(42.7)	**<0.001**
back/neck	77	(73.3)	21	(20.0)	7	(6.7)	56	(62.9)	9	(10.1)	24	(27.0)	0.120
Myalgia[b]	61	(58.1)	38	(36.2)	6	(5.7)	34	(38.6)	21	(23.9)	33	(37.5)	**0.007**
Fatigue	76	(72.4)	22	(21.0)	7	(6.7)	36	(40.4)	26	(29.2)	27	(30.3)	**<0.001**
Insomnia	78	(74.3)	22	(21.0)	5	(4.8)	41	(46.1)	21	(23.6)	27	(30.3)	**<0.001**
Sombreness[b]	92	(87.6)	10	(9.5)	3	(2.9)	54	(61.4)	19	(21.6)	15	(17.0)	**<0.001**
Loss of vitality	83	(79.0)	18	(17.1)	4	(3.8)	43	(48.3)	27	(30.3)	19	(21.3)	**<0.001**
Numbness	87	(82.9)	13	(12.4)	5	(4.8)	57	(64.0)	19	(21.3)	13	(14.6)	**0.003**
Paraesthesia	96	(91.4)	6	(5.7)	3	(2.9)	65	(73.0)	13	(14.6)	11	(12.4)	**0.001**
Nausea	95	(90.5)	7	(6.7)	3	(2.9)	67	(75.3)	15	(16.9)	7	(7.9)	**0.004**
Vomiting[c]	99	(95.2)	3	(2.9)	2	(1.9)	85	(95.5)	2	(2.2)	2	(2.2)	1.000*
Abdominal pain	96	(91.4)	6	(5.7)	3	(2.9)	73	(82.0)	12	(13.5)	4	(4.5)	0.051
Skin diseases	100	(95.2)	3	(2.9)	2	(1.9)	78	(87.6)	5	(5.6)	6	(6.7)	0.055
Hair loss	96	(91.4)	4	(3.8)	5	(4.8)	72	(80.9)	5	(5.6)	12	(13.5)	**0.032**

**Fisher's exact test; [a]p-value corresponds to the comparison of the proportion of individuals answering 'yes' (proportion of 'somewhat' and 'yes' summed) and those responding 'no' between the groups 'mildly affected' and 'highly affected'; [b]Total highly affected group n=88; [c]Total mildly affected group n=104.*

Supplementary table 3. Comparison of two possible measures for chikungunya disease persistence

		CLTCS Score			
		Recovered (4)	Mildly Affected (5-12)	Highly affected (13-20)	Total
Do you still suffer from chikungunya symptoms?	No	108 (98.2%)	40 (38.1%)	2 (2.2%)	150 (49.3%)
	Yes	2 (1.8%)	65 (61.9%)	87 (97.8%)	154 (50.7%)
Total		110 (100.0%)	105 (100.0%)	89 (100.0%)	304 (100.0%)

Supplementary table 4. Overview of participants' selection procedure

	n
Selected participants	535
Contacted participants	411
Consenting participants	339
Reasons for non-contacting	
No attempt was made when project ended, due to lack of fieldwork capacity	25
Participant was not reached by phone and visit	68
Non-participant circumstances prevented interviewer from (completing) interviewing	9
Participant was on holiday/ abroad	20
Participant died	2
Reasons for non-response	
Refusal	36
After contacting, no interview performed due to unforeseen circumstances	25
Individual had already participated in another local chikungunya study	6
Individual denied having been infected with chikungunya virus	5

Supplementary table 5. Symptoms stratified by chronic disease status

	Recovered (n=110)		Mildly affected (n=107)		Highly affected (n=89)		
	n	(%)	n	(%)	n	(%)	p-value[b]
Joint pain in the …							
upper extremities	7	(6.4)	51	(48.6)	76	(85.4)	**<0.001**
lower extremities	9	(8.2)	48	(45.7)	74	(83.1)	**<0.001**
Back/neck	8	(7.3)	35	(33.3)	41	(46.1)	**<0.001**
Weakness in the …							
upper extremities	2	(1.8)	41	(39.0)	67	(75.3)	**<0.001**
lower extremities	7	(6.4)	33	(31.4)	63	(70.8)	**<0.001**
back/neck	7	(6.4)	28	(26.7)	33	(37.1)	**<0.001**
Myalgia[b]	8	(7.3)	44	(41.9)	54	(61.4)	**<0.001**
Fatigue	13	(11.8)	29	(27.6)	53	(59.6)	**<0.001**
Insomnia	11	(10.0)	27	(25.7)	48	(53.9)	**<0.001**
Sombreness[b]	3	(2.7)	13	(12.4)	34	(38.6)	**<0.001**
Loss of vitality	7	(6.4)	22	(21.0)	46	(51.7)	**<0.001**
Numbness	0	(0.0)	18	(17.1)	32	(36.0)	**<0.001**
Paraesthesia	2	(1.8)	9	(8.6)	24	(27.0)	**<0.001**
Nausea	1	(0.9)	10	(9.5)	22	(24.7)	**<0.001**
Vomiting[c]	0	(0.0)	5	(4.8)	4	(4.5)	**0.035***
Abdominal pain[d]	2	(1.8)	9	(8.6)	16	(18.0)	**<0.001**
Skin diseases	4	(3.6)	5	(4.8)	11	(12.4)	**0.031**
Hair loss	5	(4.5)	9	(8.6)	17	(19.1)	**0.003**

**Fisher's exact test; [a]p-value corresponds to the comparison of the proportion of individuals answering 'yes' (proportion of individuals answering 'somewhat' and 'yes' summed) and those responding 'no' between the groups 'recovered', 'mildly affected' and 'highly affected' using the chi-square test; [b]Total highly affected group n=88; [c]Total mildly affected group n=104; [d]Total recovered group n=109*

Supplementary table 6. Univariate analysis of general characteristics comparing the recovered vs. the affected population

	Recovered (n=110)		Affected (n=194)		
	n	(%)	n	(%)	p-value[a]
Age					
18-40 years	36	(32.7)	30	(15.5)	
41-60 years	44	(40.0)	114	(58.8)	
>60 years	30	(27.3)	50	(25.8)	**0.001**
Sex					
Female	76	(69.1)	149	(76.8)	
Male	34	(30.9)	45	(23.2)	0.141
Education					
Illiterate/ primary school	25	(22.7)	45	(23.2)	
Secondary school	36	(32.7)	74	(38.1)	
Intermediate vocational education	33	(30.0)	47	(24.2)	
University (of applied sciences)	16	(14.5)	28	(14.4)	0.690
Occupation[b]					
Unemployed/student/housewife/voluntary	19	(17.4)	39	(20.1)	
Paid job (domestic or manual)	42	(38.5)	87	(44.8)	
Paid job (not domestic or manual)	28	(25.7)	33	(17.0)	
Retired	20	(18.3)	35	(18.0)	0.317
Income[c]					
0-999ANG	7	(6.5)	23	(12.0)	
1000-2499 ANG	40	(37.4)	81	(42.4)	
2500-4999 ANG	43	(40.2)	67	(35.1)	
>5000 ANG	17	(15.9)	20	(10.5)	0.204
Underlying chronic disease					
None	61	(55.5)	91	(46.9)	0.152
Joint disease	8	(7.3)	34	(17.5)	**0.013**
Cardiac disease[d]	20	(18.2)	53	(27.3)	0.073
Neurologic disease	4	(3.6)	7	(3.6)	1.000*
Diabetes mellitus	10	(9.1)	29	(14.9)	0.142
Other disease[e]	13	(11.8)	17	(8.8)	0.391

**Fisher's exact test; [a]p-value corresponds to the comparison between the groups 'recovered' and 'affected' (mildly and highly affected together) using the chi-square test; [b]Total recovered group n=109; [c]Total recovered group n=107, total affected group n=191; [d]Cardiac disease group includes hypercholesterolemia and hypertension; [e]Other diseases included chronic lung diseases, thyroid diseases, auto-immune diseases, gastro-intestinal complaints, pain complaints, allergies and other.*

Supplementary table 7. Univariate analysis of general characteristics comparing mildly affected vs. highly affected population

	Mildly affected (n=105)		Highly affected (n=89)		
	n	(%)	n	(%)	p-value[a]
Age					
18-40 years	17	(16.2)	13	(14.6)	
41-60 years	63	(60.0)	51	(57.3)	
>60 years	25	(23.8)	25	(28.1)	0.787
Sex					
Female	75	(71.4)	74	(83.1)	
Male	30	(28.6)	15	(16.9)	0.054
Education					
Illiterate/ primary school	24	(22.9)	21	(23.6)	
Secondary school	35	(33.3)	39	(43.8)	
Intermediate vocational education	32	(30.5)	15	(16.9)	
University (of applied sciences)	14	(13.3)	14	(15.7)	0.152
Occupation					
Unemployed/student/housewife/voluntary	18	(17.1)	21	(23.6)	
Paid job (domestic or manual)	50	(47.6)	37	(41.6)	
Paid job (not domestic or manual)	20	(19.0)	13	(14.6)	
Retired	17	(16.2)	18	(20.2)	0.497
Income[b]					
0-999ANG	16	(15.4)	7	(8.0)	
1000-2499 ANG	41	(39.4)	40	(46.0)	
2500-4999 ANG	36	(34.6)	31	(35.6)	
>5000 ANG	11	(10.6)	9	(10.3)	0.455
Underlying chronic disease					
None	60	(57.1)	31	(34.8)	**0.002**
Joint disease	14	(13.3)	20	(22.5)	0.095
Cardiac disease[c]	26	(24.8)	27	(30.3)	0.421
Neurologic disease	4	(3.8)	3	(3.4)	1.000*
Diabetes mellitus	8	(7.6)	21	(23.6)	**0.002**
Other disease[d]	6	(5.7)	11	(12.4)	0.103

**Fisher's exact test; [a]p-value corresponds to the comparison between the groups 'mildly affected' and 'highly affected' using a Chi-square test; [b]Total mildly affected group n=104, total highly affected group n=87; [c]Cardiac disease group includes hypercholesterolemia and hypertension; [d]Other diseases included chronic lung diseases, thyroid diseases, auto-immune diseases, gastro-intestinal complaints, pain complaints, allergies and other.*

Supplementary table 8. Final model of factors independently associated with being defined as chronically affected vs. recovered from chikungunya disease

	OR (CI_{95})	p-value
Arthralgia in upper extremities		
No	1	
Yes (somewhat/yes)	4.93 (1.78 – 13.64)	**0.002**
Arthralgia in lower extremities		
No	1	
Yes (somewhat/yes)	12.29 (4.86 – 31.09)	**<0.001**
Weakness in upper extremities		
No	1	
Yes (somewhat/yes)	14.93 (3.05 – 72.99)	**0.001**
Myalgia		
No	1	
Yes (somewhat/yes)	3.08 (1.11 – 8.52)	**0.030**
Age		
18-40 years	1	**0.007**
41-60 years	2.24 (0.96 – 5.22)	0.061
>60 years	0.53 (0.18 – 1.54)	0.241

Supplementary table 9. Final model of factors independently associated with being defined as highly affected vs. mildly affected by chronic chikungunya disease

	OR (CI_{95})	p-value
Arthralgia in upper extremities		
No	1	
Yes (somewhat/yes)	6.97 (2.84 – 17.10)	**<0.001**
Arthralgia in lower extremities		
No	1	
Yes (somewhat/yes)	3.28 (1.26 – 8.54)	**0.015**
Weakness in lower extremities		
No	1	
Yes (somewhat/yes)	4.23 (1.53 – 11.70)	**0.005**
Weakness in back/neck		
No	1	
Yes (somewhat/yes)	0.15 (0.05 – 0.45)	**0.001**
Loss of vitality		
No	1	
Yes (somewhat/yes)	3.45 (1.49 – 8.02)	**0.004**
Diabetes mellitus		
No	1	
Yes	3.66 (1.32 – 10.15)	**0.013**

Supplementary table 10. RAND-36 quality of life scores stratified by chronic disease status

	Recovered (n=110)		Mildly affected (n=107)		Highly affected (n=89)	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
Physical functioning	100.0 (80.0-100.0)	87.5 (21.1)	90.0 (70.0-100.0)	78.7 (25.3)	60.0 (37.5-80.0)	56.6 (28.2)
Social functioning	100.0 (87.5-100.0)	91.0 (14.1)	87.5 (75.0-100.0)	85.1 (18.3)	75.0 (62.5-87.5)	73.3 (23.4)
Physical role functioning[c]	100.0 (100.0-100.0)	90.0 (28.0)	100.0 (50.0-100.0)	75.5 (38.6)	75.0 (0.0-100.0)	55.9 (43.0)
Emotional health perceptions	100.0 (100.0-100.0)	93.3 (23.4)	100.0 (100.0-100.0)	82.2 (35.5)	100.0 (0.0-100.0)	60.7 (45.1)
Mental health	88.0 (76.0-92.0)	83.6 (12.2)	80.0 (62.0-88.0)	77.7 (14.5)	68.0 (58.0-80.0)	67.3 (20.8)
Vitality	85.0 (70.0-90.0)	80.3 (15.0)	70.0 (60.0-82.5)	70.5 (17.7)	60.0 (50.0-70.0)	59.1 (19.2)
Bodily pain	100.0 (79.6-100.0)	86.6 (21.6)	77.6 (67.3-89.8)	75.4 (20.0)	67.3 (44.9-73.5)	60.2 (20.4)
General health perception	77.5 (65.0-85.0)	74.7 (14.9)	70.0 (60.0-82.5)	69.4 (17.0)	60.0 (45.0-75.0)	57.5 (20.2)
Health change[d,e]	75.0 (50.0-100.0)	67.9 (23.6)	50.0 (50.0-75.0)	60.7 (22.4)	50.0 (25.0-75.0)	52.8 (28.6)

	Total group (n=304)		Kruskal-Wallis test	Curaçao 1996[b]
	Median (IQR)	Mean (SD)	p-value[a]	mean
Physical functioning	85.0 (55.0-100.0)	75.4 (27.8)	<0.001	89.3
Social functioning	87.5 (75.0-100.0)	83.8 (19.9)	<0.001	87.7
Physical role functioning[c]	100.0 (50.0-100.0)	75.0 (39.0)	<0.001	82.5
Emotional health perceptions	100.0 (66.7-100.0)	79.9 (37.4)	<0.001	87.4
Mental health	80.0 (68.0-88.0)	76.8 (17.2)	<0.001	78.4
Vitality	70.0 (60.0-85.0)	70.7 (19.2)	<0.001	74.6
Bodily pain	77.6 (57.1-100.0)	75.0 (23.2)	<0.001	85.1
General health perception	70.0 (60.0-80.0)	67.8 (18.6)	<0.001	68.0
Health change[d,e]	50.0 (50.0-75.0)	61.0 (25.4)	0.001	89.3

Maximum RAND-36 score for each domain= 100; IQR= 25th-75th percentile; [a]p-value corresponds to the comparison of the RAND-36 domains between the recovered, mildly affected and highly affected population using a Kruskal-Wallis test; [c](daily life) role limitations due to physical health; [b]Mean scores derived from 'the Curaçao health study' (1) [d]Total group: n=303; Recovered: n=107; [e]Indication of perceived change in health over the past year.

Reference:

1. Alberts, J. F., Gerstenbluth, I., Halabi, Y. T., Koopmans, P. C., & O'Niel, J. Heuvel van den WJA, 1996: The Curacao Health Study, methodology and main results. Assen: Van Gorcum, 119.

Supplementary file 1. Instrument.

This document is presented in the following chapter: ‘Survey instruments and interview guides’.